CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214985Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214985
PDUFA Goal Date	January 8, 2022
OSE RCM #	2021-99
Reviewer Name(s)	Timothy Bernheimer, Pharm.D.
Team Leader	Carolyn Tieu, Pharm.D., M.P.H
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	January 6, 2022
Subject	Evaluation of Need for a REMS
Established Name	daridorexant
Trade Name	Quviviq
Name of Applicant	Idorsia Pharmaceuticals, LTD.
Therapeutic Class	Orexin receptor antagonist
Formulation(s)	25 mg and 50 mg (b) (4)
Dosing Regimen	25 mg to 50 mg taken orally no more than once per night within 30 minutes of going to bed with at least 7 hours remaining prior to planned awakening. Dose adjustment of 25 mg with those with moderate hepatic impairment or taking CYP3A4 inhibitors.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Quviviq (daridorexant) is necessary to ensure the benefits outweigh its risks. Idorsia Pharmaceuticals submitted a New Drug Application (NDA) 214985 for Quviviq with the proposed indication for the treatment of adult patients with insomnia (b) (4) . The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness for the treatment of adult patients with insomnia characterized by difficulties with sleep onset, sleep maintenance, or both; however, the clinical reviewer concluded that there is not sufficient evidence (b) (4) of improvement in next day functioning (b) (4) .

The serious risks associated with Quviviq include central nervous system-depressant effects and daytime impairment; sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms; complex sleep behaviors; worsening of depression/suicidal ideation; compromised respiratory function; and the need to evaluate for co-morbid diagnoses. The risks will be communicated through the *Warnings and Precautions* section of labeling. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of Quviviq outweigh its risks. The risks associated with Quviviq are similar to other drugs in the same class (orexin receptor antagonist) and other FDA-approved medications indicated for insomnia. None of these drugs are approved with a REMS and the use of medications to treat insomnia is widely prescribed across many different specialties. As a result, likely prescribers should be familiar, knowledgeable, and able to manage the risks associated with Quviviq.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Quviviq (daridorexant) is necessary to ensure the benefits outweigh its risks. Idorsia Pharmaceuticals submitted a New Drug Application (NDA) 214985 for Quviviq with the proposed indication for the treatment of adult patients with insomnia (b) (4) . This application is under review in the Division of Psychiatry (DP). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Quviviq (daridorexant), a new molecular entity, is an orexin receptor antagonist (ORA) proposed for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

maintenance. Treatment of insomnia can range from acute to chronic, or lasting longer than three months.[b] Quviviq, proposed as 25 mg and 50 mg tablets by oral administration, is taken orally no more than once per night within 30 minutes of going to bed with at least 7 hours remaining prior to planned awakening. The mechanism of action of Quviviq is by the drug's equipotent competitive antagonism of both orexin receptors (OX1R and OX2R). Orexin A and B act on OX1R and OX2R to promote wakefulness. Quviviq is not part of a class that has a REMS or has a Boxed Warning. Quviviq is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for Quviviq NDA 214985 relevant to this review:

- 01/08/2021: NDA 214985 submitted for the treatment of insomnia (b) (4)
- 06/15/2021: A Mid-cycle Communication meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Quviviq
- 11/02/2021: A Late-cycle Communication meeting was held between the Agency and the Applicant via teleconference.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Insomnia is the dissatisfaction with sleep quantity and quality. Patients with insomnia have difficulty initiating or maintaining sleep and or the inability to return to sleep after early waking.[1]

Insomnia is the stated reason for over 5 million physician office visits in 2010 which was a 13% increase from 4.9 million visits in 1999[2] and approximately 30% to 40% of adults in the United States report symptoms of insomnia at some point in a given year.[3,c] Insomnia is more prevalent in women than men and the prevalence of symptoms generally increases with age.[4] Patients with a family history of insomnia or a previous episode of insomnia are at an increased risk.[5] Chronic insomnia and psychiatric disorders such as depression, anxiety[6], substance use disorders, and posttraumatic stress disorder[7] commonly coexist.

Societal and global health implications of insomnia is a great burden. Patients with insomnia often experience fatigue, irritability, interference with personal functioning, and impairment of attention,

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

concentration, and memory.[3,d] These symptoms impact the workforce in that professionals with insomnia are more likely to miss work, be less efficient at work, and have a higher accident rate while driving compared with good sleepers.[8] Loss of productivity due to insomnia was estimated at $63.2 billion in the United States in 2009.[9]

3.2. Description of Current Treatment Options

Predisposing factors that may cause insomnia (depression, anxiety, pain, medications, substance abuse) should be addressed. If insomnia persists despite management of predisposing factors, cognitive behavior therapy (CBT) and pharmacotherapy are the main treatment options.[9]

Cognitive behavior therapy for insomnia is a strategy that contains multiple components that address behaviors that interfere with sleep. Behavioral therapies consist of establishment of a stable bedtime/wake time schedule, relaxation training, sleep restriction, stimulus control (using bed only for sleep or getting out of bed when unable to sleep), and sleep hygiene (avoidance of substances that interfere with sleep, light, and naps).[10] Insomnia that does not respond to non-pharmacological therapies can be treated pharmacologically.

Currently approved treatments for insomnia include benzodiazepines, sedative hypnotics, melatonin agonists, doxepin, and orexin receptor antagonists.[11] Table 1 in the Appendix provides the list of medicines approved by FDA for the treatment of insomnia. Approved treatments for occasional sleeplessness include the antihistamines, diphenhydramine and doxylamine. Due to the anticholinergic effects of antihistamines, there is an increased risk of confusion and delirium in older adults and these treatments should be used cautiously.[12]

Other pharmacological treatments that are used but are not approved for insomnia by FDA include sedating anti-depressants (trazodone, mirtazapine, amitriptyline), antipsychotics (quetiapine), antiepileptics (gabapentin), antihypertensives (clonidine), other antihistamines (hydroxyzine) and other benzodiazepines (alprazolam, clonazepam, and lorazepam).[13]

Dietary supplements are used for insomnia (e.g., melatonin and valerian root) but patients and providers should consider use of these supplements carefully due to the but there are uncertainties and mixed findings observed for natural insomnia remedies.[14]

4. Benefit Assessment

The proposed indication for this application is supported by the pivotal efficacy trials ID-078A301 (Study 301) and ID-078A302 (Study 302). Both studies were identical in design: multi-center, randomized, double-blind, placebo controlled, parallel-group, Phase 3 studies.

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Both studies consisted of a screening period, followed by a placebo run in, a 3-month double-blind study, and a placebo run-out. Subjects included in both studies met the criteria for insomnia according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) and had a self-reported insomnia of at least moderate severity using the Insomnia Severity Index (ISI) score. Subjects were excluded from both studies if they self-reported daytime napping greater than 1 hour per day and more than 3 days per week, had a body mass index of < 18.5 or >40 kg/m2, were pregnant, breastfeeding, or planning to become pregnant, had any history of suicide attempt, or any other clinical evidence of any disease, medical condition or treatment that could affect the subject's safety or interfere with study assessments.

Study 301 consisted of 930 subjects with moderate to severe insomnia randomized in a 1:1:1 ratio (310 subjects in each group) to Quviviq 25, Quviviq 50 mg, or placebo that included adults with a mean age of 55.4 years with a standard deviation of 15.5 (median 59, range 18 to 88 years), majority female (67.1%) adults and elderly (39% >65 years of age) and White (90.2%) across 75 sites in 10 countries.

Study 302 consisted of 924 subjects randomized to Quviviq 25 mg (N=309), 10 mg (N=307), or placebo (N=308) that included adults with a mean age of 56.7 years with a standard deviation of 14.2 (median 59, range 19 to 85), majority female (69%), elderly (39.3% >65 years of age), and White (87.8%), across 81 sites in 11 countries.

Primary endpoints for both studies consisted of changes from baseline of two objective parameters: latency of persist sleep (LPS) and wake after sleep onset (WASO) at Month 1 and Month 3. LPS is a measure of sleep induction while WASO is a measure of sleep maintenance. LPS is the time from start of recording to the beginning of first continuous 20 epochs (10 mins) scored as non-awake as determined by PSG. WASO is defined as the time spent awake after onset of persistent sleep until lights on, as determined by PSG.

The secondary endpoints for both studies were changes from baseline in subjective total sleep time (sTST) and Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain score at Month 1 and 3. IDSIQ is a patient reported outcome assessment developed by the Applicant to assess and evaluate change in impairments in daytime functioning in patients with insomnia.

In Study 301, doses of 25 and 50 mg of Quviviq showed a statistically significant improvement vs placebo on LPS, WASO and sTST at Month 1 and Month 3. The 50 mg dose demonstrated superiority to placebo on the IDSIQ sleepiness domain score, but no significant effect was found for the 25 mg dose. At Month 1, the difference from baseline between the 50 mg and 25 mg groups compared to placebo for was -11 (95% CI: -16, -7) and -8 (95% CI: -13, -4) respectively; for WASO it was -23 (95% CI: -38, -18) and -12 (95% CI: -17, -7) respectively; and for sTST it was 22 (95% CI: 14, 30) and 13 (95% CI: 5, 20) respectively. At Month 3, the difference from baseline between the 50 mg and 25 mg groups compared to placebo for LPS was -12 (95% CI: -16, -7) and -8 (95% CI: -12, -3) respectively; for WASO it was -18 (95%CI: -24, -13) and -12 (95% CI: -12, 3) respectively; and for sTST 20 (95% CI: 11, 29) and 10 (95% CI: 1, 19), respectively. The magnitude of effect was highest with 50 mg across all endpoints.

In study 302, Quviviq 25 mg showed a statistically significant improvement vs placebo on WASO and sTST at Month 1 and Month 3. No significant effect was found for LPS and the IDSIQ sleepiness domain

score for Quviviq 25 mg. At Month 1, the difference from baseline between the 25 mg group to placebo in minutes at for WASO was -12 (95% CI: -18, -6); and for sTST was 16 (95% CI: -8, -24). At Month 3, the difference between the 25 mg group compared to placebo in minutes for WASO was -10 (95% CI: -17, -4); and for sTST was 19 (95% CI: 10, 28). Quviviq 10 mg did not show a statistically significant improvement on LPS, WASO, sTST, or IDSIQ at Month 1 or Month 3.

The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness for the treatment of adult patients with insomnia characterized by difficulties with sleep onset, sleep maintenance, or both.[e] The clinical reviewer concluded that considering only a single study and single dose supporting statistically significant improvement on the IDSIQ sleepiness domain, there is not sufficient evidence (b) (4) of improvement in next day functioning (b) (4).

Refer to the FDA NDA Integrated Review and Evaluation: NDA 214985 Quviviq (daridorexant) for more information.[15]

5. Risk Assessment & Safe-Use Conditions

The safety database of Quviviq was compiled from three placebo-controlled Phase 3 clinical studies (Studies 301 and Study 302), and a 9-month extension study (Study 303) all of which were identical in design. A total of 1847 subjects (including approximately 40% subjects being >65 years old), received Quviviq 50 mg (n=308); 25 mg (N=618); 10 mg (N=306) or placebo (N=615).

There was one death due to cardiac arrest reported in the trials that made up the safety database. This event occurred in the 25 mg treatment arm of Study 301 and the clinical reviewer concluded that although this event was treatment emergent, this subject was at a relatively high risk for a cardiovascular death, based on age and medical history.

The overall rate of adverse events leading to discontinuation was no greater than that of placebo for all active treatment arms in both study 301 and 302. The adverse events (AEs) most commonly leading to discontinuation were nervous system and psychiatric related, but no single adverse event was reported to exceed two patients.

The serious adverse event (SAE) of syncope occurred in 2 placebo-arm subjects in Study 301 and 302, and in one subject in the 50 mg arm of Study 301. The clinical reviewer states that syncope was unrelated to sedative-hypnotic effects of Quviviq in this case, and that the likely casual factors for the subject's syncope was due to a hemorrhoid operation. The clinical reviewer concluded there were fairly few serious SAEs in the Quviviq clinical program.

The *Warnings and Precautions* section of the labeling include risks of CNS-depressant effects and daytime impairment, sleep paralysis, hypnagogic/hypnopompic hallucinations and cataplexy-like

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

symptoms, complex sleep behaviors, worsening of depression/suicidal ideation, compromised respiratory function, and need to evaluate for co-morbid diagnoses (described below).[f]

5.1. CNS-Depressant Effects and Daytime Impairment

Somnolence was observed in the clinical program of Quviviq and Quviviq is a central nervous system depressant that can impair daytime wakefulness even when used as prescribed. Somnolence AEs occurred at rates of 4.5% for 50 mg vs. 6.5% for 25 mg vs. 3.6% for placebo in the safety database for Quviviq. The clinical reviewer concluded that there is little indication of a dose response in the 25 to 50 mg dose range for drug-induced somnolence AEs and the differences in rates cannot likely be explained by competing prevention of somnolence AEs by the 50 mg dose.

Class effects common to drugs labeled for the treatment of insomnia across pharmacological classes include increased risk of CNS depression with CNS depressants and an increase in the incidence of falls. Fall and injury SAEs were rare and not more common in drug than placebo arms in the Quviviq clinical program.

The clinical program for Quviviq also contained three special studies assessing effects on the ability to drive vehicles and operate machinery (ID-078-108, known as Study 108), rebound insomnia (assessed during the placebo run-out period after three months of treatment during in Study 301 and 302), and withdrawal effects (also assessed during the run-out period).

Study 108 was a randomized, double blind, placebo and active-controlled, four-way crossover study in 60 healthy middle-aged and elderly subjects. Subjects were given either daridorexant 50 mg or 100 mg once daily for four days, Zopiclone 7.5 mg on days 1 and 4 only, or placebo for four days. The primary endpoint for this study was driving performance as measured by the mean standard deviation of the lateral position (SDLP) in difference from placebo in centimeters on Days two and five at nine hours post dose. Driving ability was impaired in some subjects taking Quviviq 50 mg and the risk of daytime impairment may be increased if the drug is taken with less than a full night of sleep or if a higher than recommended dose is taken.

The findings for the risk of CNS depressant effects and daytime impairment of Quviviq are consistent with a known class effect.

The label advises healthcare professionals to counsel patients about next-day somnolence, to use caution with next day driving and other activities that require complete mental alertness and to avoid use with CNS depressants and alcohol.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5.2. Worsening of Depression/Suicidal Ideation

In the clinical program of Quviviq, depression symptoms were higher in patients receiving Quviviq than those receiving placebo. Depression occurred in 1.3% of patients in the 50 mg arm of study 301 and in 1.6% of the pooled 25 mg population. In the pooled placebo population, depression occurred in 0.5% of subjects. The clinical reviewer concludes that the depression adverse events considered likely to reflect a real drug effect, based on pharmacology and class effects. Suicidal ideation was reported in 0.2% of the pooled 25 mg population vs no reports in the pooled placebo population.

Increased suicidal ideation is a class effect observed with hypnotics and worsening of depression and suicidal thoughts have been reported with Quviviq.

The label advises healthcare providers to administer Quviviq with caution in patients with depression and to monitor suicide risk.

5.3. Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms

Sleep paralysis and hallucinations were observed in the Quviviq clinical trials. In the Quviviq clinical sleep paralysis was reported in 0.5% and 0.3% of patients receiving 25 mg and 50 mg of Quviviq compared to no reports for placebo. Hallucinations were reported in 0.8% of patients receiving 25 mg.

Parasomnia occurred in 1.6% of patients treated with 50 mg in Study 301 and occurred in 1.5% in the pooled 25 mg population. In the pulled placebo population, parasomnia occurred in 0.8% of patients. The clinical reviewer concludes that this signal belongs to an established class effect and is considered likely to reflect a true drug effect.

Though no events of cataplexy-like symptoms occurred in the Quviviq clinical program, the class effect will be described in the *Warnings and Precautions* section of the label along with the risks of sleep paralysis and hallucinations.

The label advises healthcare providers to counsel and explain these events to patients when prescribing.

5.4. Complex Sleep Behaviors

Although not observed in the Quviviq clinical trials, the risk of complex sleep behaviors is common to drugs labeled for the treatment of insomnia across pharmacological classes. Complex sleep behaviors that have been reported with other hypnotics include sleep walking, sleep-driving, and engaging in other activities while not fully awake. These events may occur after the first dose or any subsequent dose.

The label advises healthcare providers to discontinue Quviviq immediately if the patient experiences a complex sleep behavior.

5.5. Compromised Respiratory Function

Quviviq has not been studied in patients with compromised respiratory function, however this risk is common to drugs labeled for the treatment of insomnia.

The label will advise healthcare professionals to exercise caution when prescribing Quviviq to patients with compromised respiratory function.

5.6. Need to Evaluate for Co-morbid Diagnoses

The need to evaluate for co-morbid diagnoses is common to drugs labeled for the treatment of insomnia because sleep disturbances may be the presenting manifestation of a medical and/or psychiatric disorder. Worsening of insomnia or the emergence of new cognitive or behavioral abnormalities may be the result of an unrecognized underlying psychiatric or medical disorder and can emerge during the course of treatment with sleep-promoting drugs.

Schizophrenia exacerbation occurred in the 25 mg arm of Study 302. The event occurred in a patient with a prior diagnosis of schizophrenia and was unmedicated for the condition at the time. The SAE involved persecutory delusions and hallucinations with associated suicidal ideation. The clinical reviewer states that based on the clinical review of the patient's case narrative it appears that her insomnia was secondary to the psychotic disorder and does not appear to be related to drug effect. All other psychiatric SAEs occurred in the placebo arms.

The label will advise healthcare providers to only initiate treatment after careful evaluation of the patient and to reevaluate treatment if insomnia fails to improve after seven to 10 days of treatment.

6. Expected Postmarket Use

The risks of Quviviq are consistent with the risks of other medications used to treat insomnia. Quviviq will likely be used by many different types of healthcare providers in a variety of treatment settings. Insomnia can be associated with a range of comorbid medical conditions and as a result, the likely prescribers of Quviviq for the treatment of insomnia will include a broad range of specialists (e.g., primary care physicians, sleep specialists, pain management, neurologists, geriatrics and psychiatrists).[16] These prescribers should be able to monitor, diagnosis, and manage the risks and adverse events associated with Quviviq. Pharmacies that dispense Quviviq will likely include outpatient and inpatient pharmacies, integrated health systems, palliative care facilities, and long-term care facilities as the treatment of insomnia may range from acute to extended periods.

Data from the human abuse potential (HAP) study indicates potential for abuse of Quviviq is like that of zolpidem and suvorexant, both of which are under Schedule IV of the Controlled Substances Act. Worsening of sleep following discontinuation of Quviviq could be associated with the potential for dependence. As a result, FDA will recommend scheduling under Schedule IV, as recommended for other orexin receptor antagonists.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Quviviq beyond routine pharmacovigilance and labeling.

7.1. Other Proposed Risk Management Activities

The review team has determined that the following post marketing requirements (PMRs) relevant to the serious safety concerns mentioned in this review are necessary for the Applicant to complete:

1. Conduct a randomized, double-blind, placebo-controlled, middle-of-the-night safety study in females and males aged 18-65 and >65 years to assess the ability to awaken to sound in the middle of the night and postural stability and cognitive function following awakening.

Reviewer's Comments: *The Division of Epidemiology and Division of Psychiatry will review the protocol for the PMR once the protocol is received.*

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of Quviviq for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance based on the efficacy and safety information currently available.

The serious risks associated with Quviviq include CNS-depressant effects and daytime impairment, sleep paralysis, hypnagogic/hypnopompic hallucinations and cataplexy-like symptoms, complex sleep behaviors, worsening of depression/suicidal ideation, compromised respiratory function, and need to evaluate for co-morbid diagnoses. The serious risks are class-wide risks associated with the class of orexin receptor antagonists. Suvorexant and lemborexant are FDA approved drugs for the same indication as Quviviq, and none of these drugs are approved with a REMS. The risks of Quviviq are shared with these products and are currently conveyed in the *Warnings and Precautions* section of labeling of suvorexant and lemborexant.

There are other FDA-approved medications indicated for insomnia in other drug classes that also share and communicate some of these risks in the *Warnings and Precautions* section of labeling. For example: the benzodiazepines indicated for insomnia (flurazepam, temazepam, triazolam and quazepam) share the risk of complex sleep behaviors.[17-20] Flurazepam and quazepam share the risk of daytime impairment.[17, 20] Sedative hypnotics indicated for insomnia (zolpidem, zaleplon, eszopiclone and zolpidem extended release) have a box warning that communicates the risk for complex sleep behaviors.[21-24] Ramelteon shares the risk of complex sleep behaviors.[25] Doxepin shares the risk of need to evaluate for co-morbid diagnoses, complex sleep behaviors, worsening depression or suicidal thinking and CNS depressant effects.[26] None of these drugs are approved with a REMS. The risks of Quviviq are similar to approved drugs indicated for the treatment of insomnia and information about these risks is widely available. The prescribers who treat insomnia include many different medical specialties and should be knowledgeable on how to manage the risks of Quviviq.

Quviviq efficacy and safety in the treatment of insomnia is supported by two clinical studies in adult patients of which the clinical reviewer bases a recommendation of approval. This reviewer agrees with the clinical reviewer that the risk associated with Quviviq use at recommended doses of 25 and 50 mg to treat insomnia is manageable in the context of standard clinical care and that measures beyond labeling are not necessary for the benefits of Quviviq to outweigh the risks.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Quviviq to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. FDA Approved Pharmalogical Therapies for Insomnia

Product Trade Name (Generic) **Year of Approval**	**Indication**	**Dosing/Administration**	**Risk Management Approaches/Boxed Warning, Medication Guide**
Benzodiazepines			
Flurazepam[17] 1970	Treatment of insomnia characterized by difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings	Initial dose is 15 mg for women and either 15 mg or 30 mg for men. The 15 mg dose can be increased to 30 mg if necessary, for efficacy	**Boxed Warning:** concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death **Warnings and Precautions:** Next-day impairment, sleep-driving and other complex sleep behaviors
Temazepam[18] 1981	Short-term treatment of insomnia (7-10 days)	15 mg before retiring; doses can range from 7.5 mg to 30 mg	**Boxed Warning:** concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death

			Warnings and Precautions: Sleep-driving and other complex sleep behaviors
Triazolam[19] 1982	Short-term treatment of insomnia (7-10 days)	0.25 mg once daily before bedtime; maximum recommended dosage is 0.5 mg once daily	**Boxed Warning:** concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death **Warnings and Precautions:** Persistent or worsening insomnia, sleep driving and other complex behaviors, CNS manifestations, effects on driving and operating heavy machinery, patients with depression, neonatal sedation and withdrawal syndrome
Quazepam[20] 1985	Treatment of insomnia characterized by difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings	Initial dose is 7.5 mg	**Boxed Warning:** concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death **Warnings and Precautions:** Impaired alertness and motor coordination, including risk of daytime impairment; sleep-driving and other complex sleep behaviors
Hypnotics			
Zolpidem[21] 1992	Short-term treatment of insomnia characterized by difficulties with sleep initiation	Initial dose is a single dose of 5 mg for women and a single dose of 5 or 10 mg for men, immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening (maximum dose of 10 mg)	**Boxed Warning:** Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake. Some of these events may result in serious injuries, including death.

			Warnings and Precautions: Impaired alertness and motor coordination, including risk of morning impairment
Zaleplon[22] 1999	Short-term treatment of insomnia	5 mg to 20 mg immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep	**Boxed Warning:** Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake. Some of these events may result in serious injuries, including death. **Warnings and Precautions:** Next-day impairment
Eszopiclone[23] 2004	Treatment of insomnia (shown to decrease sleep latency and improve sleep maintenance)	Recommended initial dose is 1 mg, immediately before bedtime, with at least 7-8 hours remaining before the planned time of awakening (maximum dose 3 mg)	**Boxed Warning:** Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake. Some of these events may result in serious injuries, including death. **Warnings and Precautions:** Impaired alertness and motor coordination, including risk of morning impairment
Zolpidem Extended Release[24] 2005	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance	Recommended initial dose is a single dose of 6.25 mg for women and a single dose of 6.25 or 12.5 mg for men, immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening (maximum dose of 12.5 mg)	**Boxed Warning:** Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake. Some of these events may result in serious injuries, including death. **Warnings and Precautions:** Impaired alertness and motor coordination, including risk of morning impairment
Melatonin Receptor Agonists			

Ramelteon[25] 2005	Treatment of insomnia characterized by difficulty with sleep onset	8 mg taken within 30 minutes of going to bed (maximum dose 8 mg)	**No boxed warning** **Warnings and Precautions:** severe anaphylactic reactions; abnormal behavioral changes; complex sleep behaviors
Histamine Receptor Antagonist			
Doxepin[26] 2010	Treatment of insomnia characterized by difficulties with sleep maintenance	6 mg within 30-minutes of bedtime	**No boxed warning** **Warnings and Precautions**: need to evaluate for co-morbid diagnoses, abnormal thinking, behavioral changes, complex behaviors, depression, CNS-depressant effects, potential additive effects with combination with CNS depressants, patients with severe sleep apnea
Orexin Receptor Antagonist			
Suvorexant[27] 2014	Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance	10 mg, no more than once per night taken within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening (maximum dose 20 mg)	**No boxed warning** **Warnings and Precautions:** CNS depressant effects and daytime impairment, worsening of depression/suicidal Ideation, complex sleep behaviors, sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms, compromised respiratory function, need to evaluate for comorbid diagnoses.
Lemborexant[28] 2019	Treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance	Recommended dose is 5 mg taken no more than once per night, immediately before going to bed, with at least 7 hours remaining before the planned time of awakening (maximum recommended dose is 10 mg).	**No boxed warning** **Warnings and Precautions:** CNS depressant effects and daytime impairment, sleep paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms, complex sleep behaviors, compromised respiratory function, worsening

			of depression/suicidal ideation and need to evaluate for co-morbid diagnoses

10.2. References

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/s/

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